

## EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	method adj2 treatmetn adj angiogenesis	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/10/25 08:15
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L3	0	method adj treatmetn adj angiogenesis	US-PGPUB; USPAT	OR	OFF	2006/10/25 08:15
L4	0	method adj2 treatmetn adj2 angiogenesis	US-PGPUB; USPAT	OR	OFF	2006/10/25 08:15
L5	42	method adj2 treatment adj2 angiogenesis	US-PGPUB; USPAT	OR	OFF	2006/10/25 08:20
L6	339	zoledronic	US-PGPUB; USPAT	OR	OFF	2006/10/25 08:20
L7	236	I6 and (arthritis or osteoarthritis or ischemia or inflammation or psoriasis or retinopathy or macular)	US-PGPUB; USPAT	OR	OFF	2006/10/25 08:22
L8	478	(zoledronic or zoledronate) and (arthritis or osteoarthritis or ischemia or inflammation or psoriasis or retinopathy or macular)	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/10/25 10:15
L9	70	(zoledronic or zoledronate) and (arthritis or osteoarthritis or ischemia or inflammation or psoriasis or retinopathy or macular)	USPAT; DERWENT	OR	OFF	2006/10/25 09:30
L10	13	I9 and arterial	USPAT; DERWENT	OR	OFF	2006/10/25 09:30
L11	678	(zoledronic or zoledronate)	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/10/25 10:15
L12	258	I11 and (vegf or (vascular adj endothelial adj growth adj factor))	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/10/25 10:18
L13	17243	(vegf or (vascular adj endothelial adj growth adj factor))	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/10/25 10:18
L14	4981	(vegf or (vascular adj endothelial adj growth adj factor)) same (antagonist or inhibitor or blocker)	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/10/25 10:18
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L17	197	I15 and osteoarthritis	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/10/25 10:43
L18	15	I17 and (intra-arterial or arterially or intraarterial)	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/10/25 10:44
L19	18357	osteoarthritis	US-PGPUB; USPAT	OR	OFF	2006/10/25 11:02
L20	179	I19 and (zoledronic or zoledronate)	US-PGPUB; USPAT	OR	OFF	2006/10/25 11:02
L21	18	I19 and (zoledronic or zoledronate)	USPAT	OR	OFF	2006/10/25 11:03
L22	94	(zoledronic or zoledronate)	USPAT	OR	OFF	2006/10/25 11:05
L23	81	I22 and (intravenous or parenteral)	USPAT	OR	OFF	2006/10/25 11:06
L24	64	I23 and (metastasis or tumour or tumor or cancer)	USPAT	OR	OFF	2006/10/25 11:06

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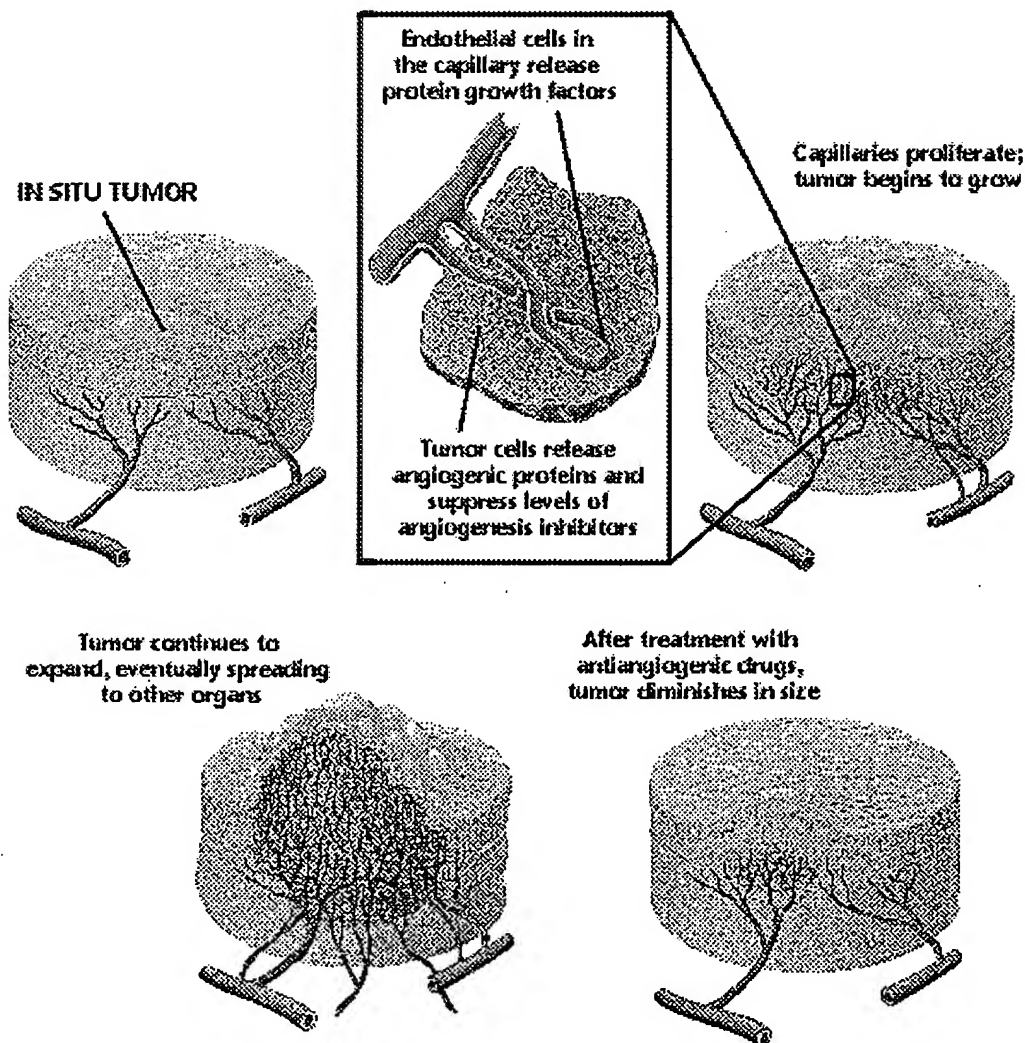
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# THERAPIES OF THE FUTURE

(from: Scientific American, September Issue 1996; by Judah Folkman)

## FIGHTING CANCER BY ATTACKING ITS BLOOD SUPPLY



Credit: Tomo Narashima

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**ANGIOGENESIS**, or neovascularization, involves the proliferation of new blood vessels. The process transforms a small, usually harmless cluster of abnormal cells (known as an in situ tumor) into a large mass that can spread to other organs. Drugs that aim to interfere with **angiogenesis**-for example, by halting the action of angiogenic proteins-can reduce the size of tumors and potentially maintain them in a dormant state.

The tiny blood vessels known as capillaries extend into virtually all the tissues of the body, replenishing nutrients and carrying off waste products. Under most conditions, capillaries do not increase in size or number, because the endothelial cells that line these narrow tubes do not divide. But occasionally-for example, during menstruation or when tissue is damaged-these vessels begin to grow rapidly. This proliferation of new capillaries, called **angiogenesis** or neovascularization, is typically short-lived, "turning off" after one or two weeks.

But neovascularization can also occur under abnormal conditions: tumor cells can "turn on" **angiogenesis**. As new blood vessels bring in fresh nutrients and proteins known as growth factors, the tumor mass can expand. In fact, neovascularization appears to be one of the crucial steps in a tumor's transition from a small, harmless cluster of mutated cells to a large, malignant growth, capable of spreading to other organs throughout the body. Tumor cells are usually unable to stimulate **angiogenesis** when they first arise in healthy tissue; unless the deranged cells become vascularized, the mass will not become larger than about the size of a pea. Thus, if researchers can determine how mutated cells trigger **angiogenesis** and, more important for patients, how to interrupt the process, they will have a powerful new anticancer therapy at their disposal. Furthermore, because antiangiogenic drugs stop new growth but do not attack healthy vessels, they should in theory do no harm to blood vessels serving normal tissues. (**Angiogenesis** inhibitors can stop menstruation or delay wound healing, however.)

Research into the importance of **angiogenesis** to the progression of cancer has been a vital area of laboratory investigation for several decades-I wrote an early article on the subject in the mid-1970s [see "The Vascularization of Tumors," by Judah Folkman; Scientific American, May 1976]. But only in the past seven years has research moved out of the laboratory and into the clinic. In 1989 the first clinical trial of an anti-angiogenic agent-interferon alpha-began for the treatment of life-threatening hemangioma (a noncancerous blood vessel tumor found primarily in infants).

By 1992 the first antiangiogenic drug for cancer patients, TNP-470 (a synthetic analogue of the substance fumagillin), entered clinical trials. The first studies were restricted to a few kinds of tumors, but the Food and Drug Administration now allows physicians to administer TNP-470 in clinical trials for a wide variety of cancers in humans. In the past four years, at least seven other **angiogenesis** inhibitors have entered clinical trials for the treatment of advanced cancer, and one of these compounds is also being tested in patients with abnormal blood vessel growth in the eyes.

The effort to explore the practical applications of antiangiogenic compounds reflects years of work by many researchers-unfortunately too numerous to list in this short space. For example, during the past several years, scientists have identified at least 14 different proteins found in the body that can trigger blood vessel growth and several others that can halt it. Most recently, researchers have discovered that one of these natural **angiogenesis** inhibitors is normally under the control of the tumor suppressor gene *p53*, which has been implicated in various cancers. With such clues, cancer researchers continue to refine their understanding of **angiogenesis** in tumor growth and of ways to block it.

## Angiogenesis Is Required for Spread

As with most aspects of cancer progression, **angiogenesis** distorts a normal biological process—in this case, regulation of blood vessel growth. Capillary blood vessels, each thinner than a hair, are arranged so that almost every healthy cell in the body can live directly on the surface of a capillary. If a healthy cell becomes cancerous and begins dividing rapidly, the resulting daughter cells accumulate in a microscopic mass. As the cells pile up, they find themselves farther and farther from the nearest capillary. When a few million such cells have accumulated, the small tumor—often called an in situ carcinoma—stops expanding and reaches a steady state, in which the number of dying cells counterbalances the number of proliferating cells. This restriction in size is caused in part by the lack of readily available nutrients, protein growth factors and oxygen. These minuscule carcinomas can be detected if they are on the skin or cervix, but in the breast, lung or colon, they may go unrecognized for several years. Regrettably, we do not yet have the technology to detect most small in situ tumors in internal organs until after the tissue has been removed and examined under a microscope.

After many months or even years in this steady state, an in situ tumor may abruptly induce new capillary growth and start to invade surrounding tissue. The tumor calls into service naturally occurring proteins that promote neovascularization. The mutated tumor cells might themselves produce high levels of such proteins; alternatively, they can mobilize angiogenic proteins found in nearby tissue, or they may prompt other types of cells, such as macrophages, to release angiogenic proteins.

Yet even after employing these mechanisms, malignant cells may still fail to trigger **angiogenesis**. Recent discoveries by Noel Bouck's group at Northwestern University and in Douglas Hanahan's laboratory at the University of California at San Francisco suggest that certain tumor cells make two types of protein: one kind stimulates **angiogenesis**, and the other inhibits it. The balance between them determines whether the tumor can switch on **angiogenesis**. And experiments indicate that the ability to turn on **angiogenesis** most likely depends on a decrease in the production of those proteins that inhibit the process. So, in effect, angiogenic cancer cells release the natural brakes on the spread of new capillaries—once a tumor becomes angiogenic, it tends to stay that way.

Once neovascularization occurs, hundreds of new capillaries converge on the tiny tumor; each vessel soon has a thick coat of rapidly dividing tumor cells. Some of these cells are not angiogenic but are nonetheless sustained by capillaries recruited by neighboring cells. Now the tumor can expand rapidly—in a matter of months, the mass may reach one cubic centimeter in size and contain around one billion tumor cells.

Further promoting the progress of the disease, the newly dividing endothelial cells release at least six different proteins that can stimulate the proliferation or motility of tumor cells. For example, in breast cancer, the capillary endothelial cells recruited to the tumor produce the protein interleukin-6, which can increase the probability that breast cancer cells will leave the tumor, migrate into the bloodstream and spread to other organs—in other words, metastasize. Some of the metastases contain cells that are already angiogenic and thus will grow rapidly. Other metastases, however, contain mainly nonangiogenic cells and may lie dormant for years, becoming angiogenic long after the original tumor has been treated or removed.

When a tumor has advanced to this stage, it often causes readily identifiable symptoms. Blood appearing between menstrual periods or in the urine, stool or sputum indicates that **angiogenesis** has taken place in the cervix, bladder, colon or lung, respectively. By the time a breast cancer can be seen on a mammogram, the tumor has already undergone vascularization. The bloody abdominal fluid seen with ovarian cancer, the bone pain of prostate cancer, the swelling around brain tumors and the obstruction of the intestinal tract common in colon cancer all result from angiogenic tumors. Biologically active molecules released by the expanding tumor can cause additional symptoms, such as weight loss and formation of blood clots.>/P>

## Shrinking Tumors

At present, patients diagnosed with any form of cancer typically rely on surgery or radiation to remove or eradicate the original tumor and on follow-up radiation or chemotherapy, or both, to try to eliminate any remaining cancerous cells in the body. Antiangiogenic therapy, in contrast to many other therapeutic approaches, does not aim to destroy tumors. Instead, by limiting their blood supply, it attempts to shrink tumors and prevent them from growing. Antiangiogenic drugs stop new vessels from forming around a tumor and break up the existing network of abnormal capillaries that feeds the cancerous mass. Currently, in addition to the **angiogenesis** inhibitors that are in clinical trials, many potential inhibitors are under study in university laboratories and in some 30 pharmaceutical and biotechnology companies around the world.

In particular, two of the compounds being looked at are very potent **angiogenesis** inhibitors, suggesting that they eventually will be quite useful for treating cancer patients. David A. Cheresh and his colleagues at the Scripps Institute discovered the first of these substances: a protein that interferes with another molecule known as an integrin, which is found in large quantities on the surface of growing endothelial cells. If the integrin (named  $\alpha v \beta 3$ ) is blocked, the proliferating endothelial cells die.

The second of these promising compounds, the protein angiostatin, was discovered in mouse urine by Michael S. O'Reilly in my laboratory at Children's Hospital Medical Center in Boston. Angiostatin is among the most potent of the known **angiogenesis** inhibitors. In animals, it can stop nearly all blood vessel growth in a large tumor or in its metastases. Human prostate, colon and breast cancers that have been implanted in mice and allowed to grow to 1 percent of the animals' body weight can be reduced to a microscopic size and held in a dormant state for as long as angiostatin is administered. Furthermore, angiostatin is very specific, halting only the multiplication of endothelial cells and not of other cells or of normally quiescent endothelial cells. This specificity has powerful benefits: researchers have not detected in animals any toxic side effects of the drug. In addition, resistance to angiostatin does not appear to develop in animals.

Angiostatin is actually a fragment of the larger protein plasminogen, which is not antiangiogenic itself. Indeed, several **angiogenesis inhibitor** proteins exist as internal fragments of larger proteins (for instance, another **inhibitor** is a fragment of the protein prolactin), suggesting that normal **angiogenesis** inhibitors may be, in a sense, stored within larger proteins. Thus, when the body needs to stop normal **angiogenesis**-after wound healing or ovulation-these natural inhibitors may be available for immediate use by simply breaking down the larger proteins.

## Offering Treatment

Laboratory studies as well as ongoing clinical trials of **angiogenesis** inhibitors provide important guidelines for how these drugs may eventually be used in cancer patients, if they receive approval from the FDA. For example, when **angiogenesis** inhibitors are first introduced into clinical practice, they will most likely be used in combination with current conventional therapy. Beverly A. Teicher of the Dana-Farber Cancer Institute in Boston has shown in animals that combinations of **angiogenesis** inhibitors and chemotherapeutic agents are more effective than either therapy alone. In one instance, 42 percent of the animals were cured by a combination of treatments but not by either drug alone.

A possible explanation for the apparent synergism between these two therapies is that the two types of cells in a tumor-the endothelial cells and the tumor cells-respond differently to therapy. For example, endothelial cells have a low or virtually undetectable mutation rate as compared with that of tumor cells and thus do not usually become drug-resistant. In addition, every 10 to 100 new tumor cells require at least one new endothelial cell. (One gram of tumor contains approximately 20 million endothelial cells and 100 million to one billion tumor cells.) Therefore, when an **angiogenesis inhibitor** halts the growth of one endothelial cell, the effect on tumor cells may be amplified.

**Angiogenesis** inhibitors have also been studied in conjunction with radiation therapy. Oncologists and radiologists initially debated whether radiation therapy would be enhanced by coupling it with antiangiogenic drugs. But Teicher recently found that treatment of mouse tumors with **angiogenesis** inhibitors did increase the effectiveness of radiation therapy. Several antiangiogenic drugs, including TNP-470 and minocycline (a relative of the antibiotic tetracycline), are being examined in conjunction with radiation therapy in animals.

After the completion of conventional chemotherapy or radiation therapy, **angiogenesis** inhibitors might be used as a long-term treatment against cancer. If the cancer has metastasized, antiangiogenic therapy may be needed indefinitely. In other situations, antiangiogenic drugs may be given for a brief period, perhaps before surgical removal of a large tumor. Antiangiogenic treatment could possibly be administered intermittently, even for a few months or years, to maintain a tumor's dormancy. Fortunately, the general lack of drug resistance developed against these compounds as well as their low toxicity makes them amenable to extended use.

## Future Directions

Although scientists have been investigating **angiogenesis** for more than two decades, many questions remain about the process, how it is regulated and how it can be controlled therapeutically. For instance, no one understands why some tumors, particularly in the cervix, undergo neovascularization much earlier than others. And antiangiogenic drugs now in development face the traditional uncertainties of all clinical trials: unforeseen side effects could surface, or a drug might be **ineffective** in humans despite its efficacy in mice.

In addition, as with any new drug, there are potential economic hurdles to overcome. Many of the **angiogenesis** inhibitors are newly discovered proteins or other types of molecules. Chemists must now figure out how to make these compounds on a large scale. This process can be expensive, but experience suggests that prices should fall with time.

Despite the obstacles, antiangiogenic substances offer the promise of an additional anticancer therapy for our current armamentarium. **Angiogenesis** inhibitors may turn out to have significant benefits because they are not as likely to induce resistance and because they generally have fewer side effects. These agents may also be used to treat other diseases characterized by abnormal **angiogenesis**. Among these other conditions are diabetic retinopathy, macular degeneration and neovascular glaucoma—all diseases of the eye in which abnormal vessels proliferate and destroy vision. In addition, psoriasis, arthritis, hemangioma and other benign tumors may be susceptible to treatment with **angiogenesis** inhibitors. Clearly, then, antiangiogenic drugs have exciting potential as therapies for a number of serious conditions—in addition to cancer.

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## Further Reading

Barriers to Drug Delivery in Solid Tumors. Rakesh K. Jain in *Scientific American*, Vol. 271, No. 1, pages 58-65; July 1994.

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The Author JUDAH FOLKMAN is director of the surgical research laboratory at Children's Hospital Medical Center of Harvard Medical School. His laboratory reported the first purified angiogenic molecule and the first **angiogenesis inhibitor**. Folkman's group then proposed the concept of angiogenic disease. Folkman is a fellow of the American Academy of Arts and Sciences and a member of the National Academy of Sciences. The author gratefully acknowledges the nearly uninterrupted support of **angiogenesis** research for more than 25 years by the National Cancer Institute.

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